The Benzodiazepines, Raven Press, New York © 1973

SUBCELLULAR ACTIONS OF BENZODIAZEPINES

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Cell Fractionation Methodology

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I. INTRODUCTION

The central action of benzodiazepines has been given limited selective review (Randall, 1961, 1968) regarding their pharmacological properties and behavioral effects, but few consistent data have been provided concerning the effects of these compounds upon central nervous system metabolism. One of the several problems encountered in the study of the central action of benzodiazepines concerns the relationship between the uptake and deposition of such molecules and the specific locus where their central effects occur and through which their functions are modulated. This series of studies investigated several neurochemical changes associated with the action of two benzodiazepine compounds. Previous behavioral indications and studies of time course for central uptake, following parenteral administration, served as a basis for consideration of their action in terms of central synaptic localization and function.

Preliminary investigations in our laboratory suggested that the guinea pig was maximally sedated 60 min following the parenteral injection of chlordiazepoxide (CDP) in doses up to 10 mg/kg. It was further established that at these times maximum drug recovery (as measured from brain tissue by low-temperature spectrofluorescence assay following heptane-alcohol and ethyl acetate extraction from regional brain-tissue homogenates) was from the cerebral cortex, which represents a substantial proportion of the total brain weight of the guinea pig. On the basis of these preliminary findings and with the operating premise that CDP and related benzodiazepines probably exert profound central synaptic actions in bringing about their other physiological and behavioral effects, several indexes of such cerebral synaptic function were utilized as measures of CDP action, including electrolyte concentration and distribution, ribonucleic acid (RNA) content, and acetylcholine (ACh) levels.

Specific concern was given to the effects of two benzodiazepine compounds, CDP and SCH 12041, upon synaptosomal elements and subcellular